UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/723,795 | 11/26/2003 | Claudiu Supuran | MST-2393 U.S. | 9070 |

24988 7590 09/07/2007

LEONA L. LAUDER
235 MONTGOMERY STREET, SUITE 1026
SAN FRANCISCO, CA 94104-0332

| EXAMINER | |
|---|---|
| FETTEROLF, BRANDON J | |
| ART UNIT | PAPER NUMBER |
| 1642 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/07/2007 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

deeopat@pacbell.net
LLLpat@pacbell.net
jharland@pacbell.net

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/723,795 | SUPURAN ET AL. | |
| | Examiner | Art Unit | |
| | Brandon J. Fetterolf, PhD | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *67-70 and 72-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-70 and 72-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/27/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

The Amendment filed on 7/06/2007 in response to the previous Non-Final Office Action (7/27/2007) is acknowledged and has been entered.

Claims 67-70 and 72-90 are currently pending and under consideration.

### *Information Disclosure Statement*

The Information Disclosure Statement filed on 6/27/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

**Rejections Maintained:**

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-70 and 72-84 remain rejection and new claims 85-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing cancer and/or hypoxia in a tissue and in vivo imaging of a tumor and/or hypoxic tissue in a patient comprising administering a labeled antibody which specifically binds CA IX, wherein overexpression of CA IX is indicative of cancer, does not reasonably provide enablement for a method of diagnosing cancer and/or hypoxia in a tissue and in vivo imaging of a tumor and/or hypoxic tissue in a patient comprising administering a CA-IX specific inhibitor selected from compounds 1-91. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands

states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

***The nature of the invention***

The claims are drawn to a method of imaging a tumor and/or hypoxic tissue in a patient comprising administering a CA IX specific inhibitor, wherein overexpression of CA IX as compared to a control sample is indicative of a precancerous or cancerous condition. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

***Level of skill in the art***

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

***The breadth of the claims***

Applicants broadly claim a method of diagnosing cancer and/or hypoxia in a tissue and an in vivo method of imaging of a tumor and/or hypoxic tissue in a patient comprising administering a CA IX specific inhibitor and detecting the binding of CA-IX specific inhibitor, wherein overexpression of CA IX as compared to a control is indicative of cancer. The claims are further drawn to CA-IX specific inhibitors selected from a group consisting of compounds 1-91.

***Guidance in the specification and Working Examples***

The specification teaches that the expression of CA IX is restricted to only few normal tissues, but is tightly associated with tumors, wherein it is also regulated by cell density in vitro and is strongly induced by tumor hypoxia in vitro and in vivo (page 2, lines 10-12). As such, the specification teaches that certain carbonic anhydrase inhibitors which are specific for CA-IX would be useful for diagnostic/prognostic methods including imaging methods, such as scintigraphy and for gene therapy (page 9, lines 23-31). With regards to the CA-IX specific inhibitors, the specification teaches the generation of 91 heterocyclic and aromatic sulfonamides and screening assays showing the inhibition of CA-IX protein (CA-IX protein also referred to as MN protein) (page 42 and 47, line 27 to page 50, line 25). Moreover, the specification teaches a comparison of CA-IX specific inhibitor, e.g., compounds 71-91, with other CA isozymes, wherein all compounds

appeared to act as inhibitors of CA isozymes , I, II, and IV, as well as the claimed CA IX (page 50, line 26 to page 52, line 30). Thus, while the specification clearly teaches that the instant compounds are successful inhibitors of the claimed CA IX isozyme, as well as CA isozymes, I, II and IV, the specification does not appear to provide a nexus between the use of these CA-IX specific inhibitors for the diagnosis of cancer. In other words, the specification does not appear to reasonably convey that the inhibitors would specifically recognize CA-IX in tumors, as compared to the tissues expressing other CA isozymes. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

***Quantity of experimentation***

The quantity of experimentation in the areas of cancer diagnosis is extremely large given the unpredictability associated with the presence of various carbonic anhydrase isozymes (CAIs) being present in both normal as well as cancerous tissues, and the lack of correlation between inhibitor specificity and diagnosis

***The unpredictability of the art and the state of the prior art***

The state of the art at the time of filing was such that one of skill could recognize that there is a relationship between CA IX expression and a tumor. For example, Zavada et al. (6,027,887, 2000, IDS) teaches that abnormal MN (also referred to as CA IX) expression is a useful diagnostic marker for neoplastic disease because very few normal tissues have been found to express MN protein to any significant degree (column 2, lines 59-61). In particular, Zawada et a. teach that MN protein is overexpressed in a variety of neoplastic disease including, but not limited to, carcinomas of the mammary, prostate, bladder, renal, ovarian, gastrointestinal, uterine and cervical, wherein very few normal tissues have been found to express (column, 3, line 54 to column 4, line 10). Along the same lines, Loncaster et al. (Cancer Research 2001; 61: 6394-6399) discloses that there is a relationship between tumor hypoxia and CA IX expression in human tumors; and that the extent of CA IX expression is a prognostic indicator of a patients outcome (page 6394, 2nd column, 1st full

paragraph). In addition to a correlation between CA IX expression and tumor development, the state of the art at the time of filing was such that one of skill could recognize that the CA IX isozyme is not the only carbonic anhydrase expressed in malignant tissue. For example, Parkkila et al. (PNAS 2000; 97: 2220-2224) teach that immunohistochemical studies have indicated that CA II and CA XII are is expressed in renal cancer cell lines (page 2222, Figure 4). In addition to CA II expression in renal cancer cell lines, Parkkila et al. teach that CA II is also highly expressed in several other tumors, including malignant brain tumors and gastic and pancreatic carcinomas (Page 2220, 1st column, 2nd full paragraph). Regarding the brain tumors, Parkkila et al. (Histochemical Journal 1995; 27: 974-982) teaches that immunohistochemical analysis has demonstrated that CA II is highly expressed in brain tumors. Specifically, Parkkila et al. found that the most malignant tumor exhibited the strongest staining (pages 977-979, Figures 1 and 2). Thus, while Parkkila et al. found high expression levels of CA II in brain tumors, Parkkila et al. teach that since CA II is expressed in various types of neoplastic cells, CA II can not be used as a specific marker for any tumor in neuropathology (page 981, 1st column, 1st full paragraph).

Unlike the references cited above which used immunohistochemical techniques, e.g, antibodies specific for each CA isozyme, for determing CA expression patterns, the instant claims are drawn to method of diagnosis and/ or imaging using CA IX specific inhibitors, wherein the inhibitors encompass aromatic and heterocyclic sulfonamide derivatives. However, those of skill in the art recognize the unpredictability of generating inhibitors specifically for one isozyme of CA. For example, Supuran et al. (Expert Opinion on Therapeutic Patents 2000; 10: 575-600) teach that inhibition of carbonic anhydrases by aromatic/heterocyclic sulfonamides have been exploited in therapy for years. In particular, Supuran et al. teaches that carbonic anhydrase inhibitors have been shown to be useful as diuretics and the treatment an prevention of a variety of diseases such as glaucoma, epilepsy, congestive heart failure, mountain sickness, gastric duodenal ulcers, neurological disorders and osteoporsis, among others (page 576, 2nd column, last paragraph to page 577, 1st column, 1st few lines). However, despite the amount of research that has gone into the construction of CA specific inhibitors, Supuran et al. teach that CA isozymes, such as cytosolic CA I, II and VII, the membrane bound forms CA IV, IX, XII and XIV, or the mitochondrial CA V, show high or very high and similar affinities (in the micro to nanomolar range) for sulphonamide inhibitors which is not a desired situation since inhibition of CAs in sites other than the target organ/tissue may

induce undesired side effects of sulphonamide drugs (page 577, 1st column, 6th line from bottom to 2nd column, 5th line). In addition to the development of CA specific inhibitors for the treatment of variety of disorders associated with CA expression, Supuran et al. further contemplates the use of CAIs as diagnostic tools (page 588, 2nd column). In particular, Supuran teaches the possible benefits of using CA inhibitors in both MRI and PET methods for testing cerebrovascular diseases, but cautions that little previous work has been done in this field.

***Conclusion***

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation between CA IX inhibitor specificity and diagnosis of cancer, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

In response to this rejection, Applicants assert that according to the claimed methods as amended, the Specification combined with conventional knowledge provides sufficient enablement that the inhibitors in the claimed methods would specifically recognize CA IX in tumors, as compared to other CA isozymes that are expressed in normal tissue. As such, Applicants assert that the additional experimentation necessary to perform the diagnostic/prognostic methods of the claims as amended would be merely routine. In particular, Applicants assert that, for diagnostic and prognostic purposes, preferential inhibition of CA IX inhibition of CA IX over CA II and CAIV should be sufficiently enabling from CA IX specific inhibition in almost all tissues expressing CA isozymes other than CA IX because the other CA isozymes are restricted to specific tissues, have low affinity to sulfonamides or moderate to low catalytic activity. As such, an enzyme-screening assay as claimed would be routine in the art of diagnosis of cancer, and such enzymatic screening assay provide sufficient enablement. Applicants further address the following points: 1) Specificity of CA inhibitors for CA IX; 2) Correlation between CA IX inhibitor binding with Cancer Diagnosis; 3) Prior Art and CA IX-Specific Inhibitors; and 4) Requirement for working Examples in an

unpredictable art. With regards to the 1), e.g., specificity of CA inhibitors for CA IX, Applicants assert that the CA IX specific inhibitors need only be shown to be potent and preferential CA IX inhibitors for the claimed methods to be sufficiently enabled, wherein one of skill in the art would know that potent and preferential inhibition of a specific isozyme, rather than exclusive inhibition of a specific isozyme, can be sufficient to override the effects of possible inhibition of other isozymes, whether for therapeutic or diagnostic purposes. With regards to potency, Applicants assert that it is conventional in the art of drug design to consider a lead compound with nanomolar inhibition of a target enzyme a potential candidate for clinical trials (Anderson (Chemistry & Biology 2003; 10: 787-797), wherein the specification (Tables 1-3) show that a number of those 91 sulfonamides are potent nanomolar inhibitors of CA IX. With regards to the selectivity, Applicants assert that it is also conventional knowledge that, for any particular candidate inhibitor, if its selectivity for a target isozyme versus a physiologically necessary isozyme is high (as determined by relative $K_I$s), that candidate inhibitor could be used be used at a dose low enough to inhibit the targeted isozyme in vivo with minimal effects. For example, Applicants assert that the instant specification teaches that, among compounds 1-91, several demonstrate a high preference for CA IX over any of the three other CA isozymes tested, including the physiologically most important isozymes CA II and CA IV. In addition to the selectivity and potency, Applicants assert that membrane impermeant compounds that preferentially inhibit CA IX over CA IV are doubly selective for CA IX since CA isozymes found in the cytosol or mitochondria (e.g., CA I, CA II, CA III, CA V and CA VII) are not accessible to membrane impermeant compounds. With regards to 2, e.g., the correlation between CA IX inhibitor binding with cancer diagnosis, Applicants assert that the amended claims require a potent and preferential inhibitor of CA IX over other CA isozymes as determined by enzymatic screening assays. In addition, Applicants contend that passage from the specification provides a clear nexus between the screened inhibitors and cancer diagnosis. With regards to 3, e.g., Prior Art and CA IX specific inhibitors, Applicants assert that while Supuran teaches that inhibition of CAs in sites other than the target organ/tissue may induce undesired side effect of sulfonamide drugs, Supuran, in the following sentence, teaches that "Even so, sulfonamides CAIs have a firm place in medicine, mainly as antiglaucoma or antisecretory drugs. As such, Applicants assert that if the side effects of such sulfonamide CAIs are acceptable for diseases such as glaucoma, that one of skill in the art could assume that similar side effects would be acceptable for sulfonamide CAIs used to treat

cancer. Moreover, Applicants assert that one of skill would reasonably expect certain organic aromatic and heterocyclic compounds to inhibit preferentially CAIX, that is, have a lower KI than for the other isozymes. Applicants further contend that while Parkkila (1995) undertakes a study to elucidate whether the expression of CA II continues in various brain tumors, the present invention concerns an established associated of the presence of CA IX with cancer. With regards to 4, e.g., requirement for working examples in an unpredictable art, Applicants point out that at the time of filing an application, an applicant need not have any examples proving a claimed utility. Applicants further contend that one of skill in the art of cancer diagnosis would have a reasonable expectation that a potent CA IX-selective sulfonamide inhibitor, found to bind the CA domain in vitro with high affinity and with greater affinity for CA IX than any other isozyme, i.e., CA I, II or IV, would also selectively bind CA IX present on the surface of cells.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner acknowledges and appreciates Applicants amendments to the instant claims to further define the CA IX specific inhibitors as those having a Ki determined to be less than about 50 nM. However, the Examiner recognizes that the amendments, the teachings of the specification and the arguments set forth above do not appear to overcome the instant enablement rejection. For example, while Applicants contend that the CA IX specific inhibitors need only be shown to be potent and preferential CA IX inhibitors for the claimed methods to be sufficiently enabled, the Examiner recognizes that Supuran et al. appears to teach the opposite. For example, as noted in the prior office action, Supuran teach that CA isozymes, such as cytosolic CA I, II and VII, the membrane bound forms CA IV, IX, XII and XIV, or the mitochondrial CA V, show high or very high and similar affinities (in the micro to nanomolar range) for sulphonamide inhibitors which is not a desired situation since inhibition of CAs in sites other than the target organ/tissue may induce undesired side effects of sulphonamide drugs. Thus, in view of the teachings of Supuran et al., one of ordinary skill in the art would recognize that a more than preferential affinity for CA IX would be needed to practice the claimed invention. Similarly, regarding Applicants assertions with respect to the teachings of the specification and its relation to potency and specificity, the Examiner acknowledges and agrees with Applicants that some of the 91 sulfonamide inhibitors had nanomolar affinity towards CA IX. However, the Examiner recognizes that many of these "CA IX specific" inhibitors also have similar affinities and in some instances

higher affinities for other CA isozymes. For example, the specification teaches that compounds 14-21 all had nanomolar affinities for CA IX, as well as for CA II, below 50 nanomolar. Regarding Applicants assertion with respect to CA IX specific inhibitors and cancer diagnosis, the Examiner acknowledges that the claims require a potent and preferential inhibitor of CA IX. However, the Examiner recognizes that although Applicants contemplate and claim an in vivo method of imaging and diagnosis, the specification appears to be silent on any working examples. Moreover, the specification has not taught the amount of necessary for successful diagnosis or imaging, the number of times the inhibitor needs to be administered or the most appropriate route of administration. Thus, while the absence of working examples should never be the sole reason for rejecting a claim as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer or in vivo diagnosis or imaging of cancer, is required for practice of the claimed invention. Regarding Applicants assertions with respect to the prior art cited by the Examiner, the Examiner acknowledges that Supuran et al. teach that sulfonamides have a firm place in medicine, mainly as antiglaucoma or antisecretory drugs. However, the Examiner recognizes that while Supuran teaches that sulfonamides have a firm place in medicine, Supuran clearly cautions the use of CA inhibitors due to CA isozymes, such as cytosolic CA I, II and VII, the membrane bound forms CA IV, IX, XII and XIV, or the mitochondrial CA V, having high or very high and similar affinities (in the micro to nanomolar range) for sulphonamide inhibitors and further, that while CA inhibitors may be useful in both MRI and PET methods for testing cerebrovascular diseases, little previous work has been done in this field. Regarding Applicants assertions with respect to the Parkkila et al., the Examiner acknowledges Applicants opinions relating to the Parkkila et al. references. However, the Examiner recognizes that Applicants appear to have taken the teachings of Parkkila et al. out of context because these references were cited to show that other CA isozymes are found in malignant tissues, as well as normal tissues; and not intended to compare the other isozymes of CA directly with CA IX. Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation between CA IX inhibitor specificity and diagnosis of cancer, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 74-75 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 9-10, 12-18 and 31-32 of copending Application No. 11/222,986. Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus.

The method of diagnosing a preneoplastic/neoplastic disease associated with abnormal MN/CA IX expression comprising contacting a sample with a specific inhibitor of MN/CA IX, wherein the inhibitor is a compound from 1-92 or an antibody claimed in the conflicting patent application appears to fall with in the same scope of a method of diagnosing a preneoplastic/neoplastic disease associated with abnormal expression of MN/CA IX expression comprising contacting a sample with a specific inhibitor of MN/CA IX claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response to this rejection, Applicants assert that the claims as amended are patentably distinct from those of the '986 application. In particular, Applicants assert that the claims are

directed to a cell membrane impermeant aromatic or heterocyclic sulfonamide selected from compounds 1-91 and further comprising contacting a sample with an inhibitor which has been screened for potency against and selectivity for CA IX enzymatic activity.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants assertions, the Examiner acknowledges that Applicants have amended the instant claims to recite the limitations. However, the Examiner recognizes that the compounds claimed in the '986 application appear to be identical to those claimed, e.g., compounds 1-91, and further, the currently claimed invention is drawn to a method of diagnosing comprising the actice steps of contacting a sample with a CA IX specific inhibitor which is clearly taught in the pending application. Thus, the compound identified though screening has not been given any patentable weight in view of the compounds being the same as the pending application and the pending application teaching the active steps involved for diagnosis.

Therefore, No claim is allowed.

***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Supuran et al. (Curr. Med. Chem.-Imm., Endoc. & Metab. Agents 2001; 1: 61-97) teaches carbonic anhydrase inhibitors. In particular, Supuran et al. teach aromatic and heterocyclic sulfonamide inhibitors and contemplates the use for diagnosis (page 85, 2nd column 3.6). However, Supuran et al. does not teach in vivo administration of the aromatic heterocyclic inhibitors for cancer diagnosis.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600